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[54] **4-PHENYLPIPERIDINE COMPOUNDS FOR TREATING DEPRESSION**

[75] Inventors: **Franciscus Bernardus Gemma Benneker**, Nijmegan; **Frans Van Dalen**, Neunen; **Jacobus Maria Lemmens**, Mook; **Theodorus Hendricus Antonium Peters**, Arnhem, all of Netherlands; **Frantisek Picha**, Brno, Czechoslovakia

[73] Assignee: **Synthon B. V.**, Nijmegen, Netherlands

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[52] **U.S. Cl.** 514/321; 514/317; 514/319; 546/197; 546/198; 546/205; 546/206; 546/236

[58] **Field of Search** 546/197, 198, 546/205, 206, 236; 814/317, 319; 514/321

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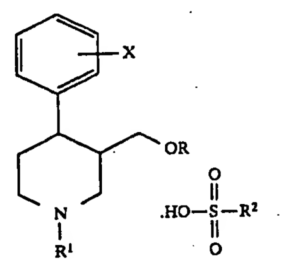
Primary Examiner—Ceila Chang
Attorney, Agent, or Firm—Howrey & Simon

[57] **ABSTRACT**

The invention relates to a compound, and pharmaceutically acceptable salts, having the formula I:



wherein:

R represents an alkyl or alkynyl group having 1–4 carbon atoms, or a phenyl group optionally substituted by C_{1-4} alkyl, alkylthio, alkoxy, halogen, nitro, acylamino, methylsulfonyl or methylenedioxy, or represents tetrahydronaphthyl,

R^1 represents hydrogen, trifluoro (C_{1-4}) alkyl, alkyl or alkynyl,

X represents hydrogen, alkyl having 1–4 carbon atoms, alkoxy, trifluoroalkyl, hydroxy, halogen, methylthio or aralkoxy,

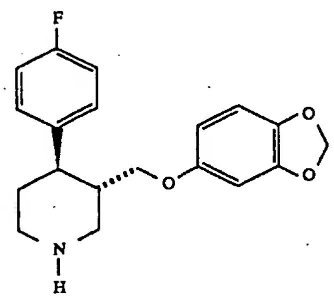
R^2 represents:
a C1–C10 alkyl group,
a phenyl group optionally substituted by one or more of the following groups:
a C1–C10 alkyl group,
a halogen group,
a nitro group,
hydroxy group,
and/or an alkoxy group.

29 Claims, No Drawings

4-PHENYLPIPERIDINE COMPOUNDS FOR TREATING DEPRESSION

The present invention relates to a group of tri-substituted, 4-phenylpiperidines, to a process for preparing such compounds, to a medicament comprising such compounds, and to the use of such compounds for the manufacture of a medicament.

The compound paroxetine, trans-4-(4'-fluorophenyl)-3-(3',4'-methylene dioxyphenoxymethyl) piperidine having the formula below:



is known and has been used in medicaments for treating, amongst other ailments, depression.

Paroxetine has been used as a therapeutic agent in the form of a salt with pharmaceutically acceptable acids. The first clinical trials were conducted with the acetate salt.

A known useful salt of paroxetine is the hydrochloride. This salt is considered to be the active substance in several marketed pharmaceutical products, e.g. Paxil or Seroxat. A number of forms of paroxetine hydrochloride have been described:

- the anhydrous form in several crystalline modifications (PCT Appl. WO 96/24595);
- the hydrated form—a hemihydrate (EP 223403) and in the solvated forms.

The comparison of behaviour between anhydrous and hydrated form of paroxetine hydrochloride is described in the Intl. Journal of Pharmaceutics 42, 135–143 (1988).

EP 223403 discloses paroxetine hydrochloride hemihydrate and pharmaceutical compositions based thereon.

Most of these known salts of paroxetine have unsuitable physico-chemical characteristics for ensuring safe and efficient handling during production thereof and formulation into final forms, since they are unstable (acetate, maleate) and possess undesirable hygroscopicity.

Furthermore their formation by crystallization from both aqueous or non-aqueous solvents is generally low-yielded and troublesome as they usually contain an undefined and unpredicted amount of bound solvent which is difficult to remove.

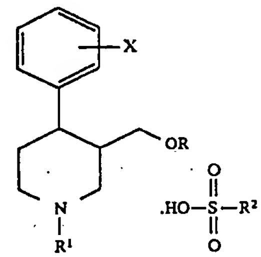
The crystalline paroxetine hydrochloride hemihydrate approaches these problems, but as stated in WO 95/16448, its limited photostability causes undesired colouration during classical wet tabletting procedure.

Moreover, crystalline paroxetine hydrochloride hemihydrate exhibits only limited solubility in water.

It has been generally suggested that where the aqueous solubility is low, for example less than 3 mg/ml, the dissolution rate at in vivo administration could be rate-limiting in the absorption process. The aqueous solubility of the paroxetine hemihydrate at room temperature exceeds this threshold by a relatively small margin.

An object of the present invention is to provide a compound with improved characteristics.

According to a first aspect, the present invention comprises a compound, and pharmaceutically acceptable salts, having the formula I:



R represents an alkyl or alkynyl group having 1–4 carbon atoms, or a phenyl group optionally substituted by C_{1-4} alkyl, alkylthio, alkoxy, halogen, nitro, acylamino, methylsulfonyl or methylenedioxy, or represents tetrahydronaphthyl,

R^1 represents hydrogen, trifluoro (C_{1-4}) alkyl, alkyl or alkynyl,

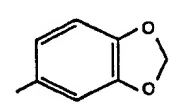
X represents hydrogen, alkyl having 1–4 carbon atoms, alkoxy, trifluoroalkyl, hydroxy, halogen, methylthio or aralkoxy,

R^2 represents:

- a C1–C10 alkyl group,
- a phenyl group optionally substituted by one or more of the following groups:
- a C1–C10 alkyl group,
- a halogen group,
- a nitro group,
- hydroxy group,
- and/or an alkoxy group.

The inventors have found that these compounds exhibit good stability and very high solubility. This yields the advantage that high concentrations of the compound are obtainable in small volumes.

The R group is preferably the 3,4 methylenedioxyphenyl group of the formula:

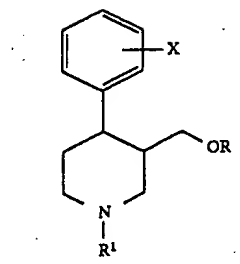


The X group is preferably a fluorine group attached to position 4 in the phenyl ring.

The R^2 group preferably represents a C1–C4 alkyl group, and most preferably represents a C1–C2 alkyl group in order to provide an optimum solubility.

The compounds can have a solubility at about 20° C. of at least about 10 mg/ml water, preferably having a solubility in water of at least 100, for example 500 and most preferably of at least 1000 mg/ml water.

According to a second aspect of the present invention, there is provided a process for preparing a compound as above, comprising the steps of mixing together a 4 phenylpiperidine compound, a salt and/or a base thereof having the formula II:



wherein:

- R represents an alkyl or alkynyl group having 1–4 carbon atoms, or a phenyl group optionally substituted by C_{1-4} alkyl, alkylthio, alkoxy, halogen, nitro, acylamino, methylsulfonyl or methylenedioxy, or represents tetrahydronaphthyl,
- R_1 represents hydrogen, trifluoro (C_{1-4}) alkyl, alkyl or alkynyl,
- X represents hydrogen, alkyl having 1–4 carbon atoms, alkoxy, trifluoroalkyl, hydroxy, halogen, methylthio or aralkoxy,

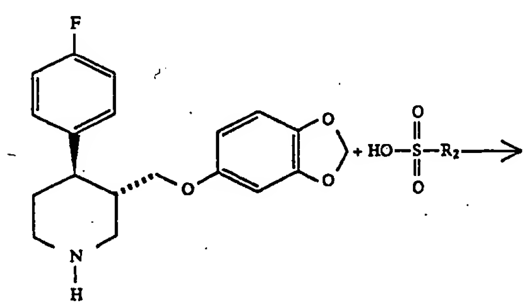
with a sulfonic acid of the general formula R_2-SO_3H, wherein R_2 represents:

- a C1–C10 alkyl group,
- a phenyl group optionally substituted by one or more of he following groups:
- a C1–C10 alkyl group,
- a halogen group,
- a nitro group,
- a hydroxy group, and/or
- an alkoxy group,

to form a solution, followed by separating the compound formed from this solution.

The compounds of the invention can be prepared from the free base of the 4 phenylpiperidine, having the formula II, this preferably being paroxetine, by treatment with a sulfonic acid as defined above in a suitable solvent to form a solution of the desired acid addition salt, whereafter this is precipitated out of the solution.

The equation for paroxetine free base and sulfonic acids is as follows:



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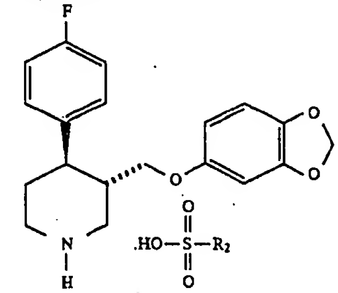
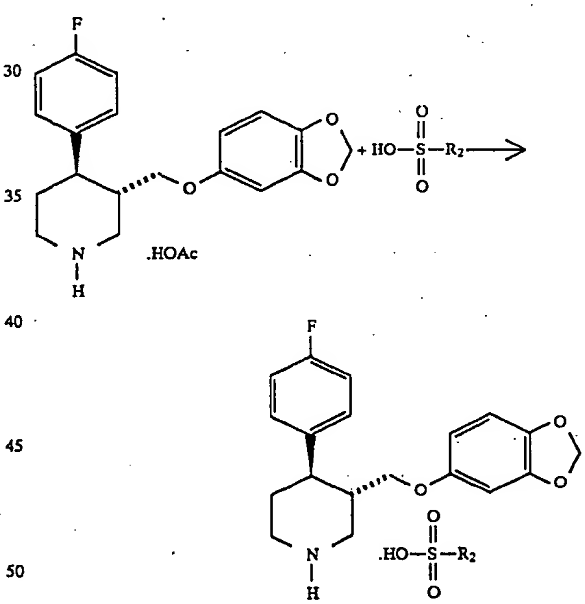


The forming of a solution may preferably proceed at temperatures from about 0° C. to the boiling point of the solvent.

Optionally, the solution may be purified by treatment of activated charcoal, silica gel, kieselguhr or other suitable materials.

Alternatively, the solution of a salt of the invention can be formed by dissolution of a salt of 4 phenyl piperidine having the formula II with an organic sulfonic acid.

For example the compounds of the invention may be prepared from a paroxetine C1–C5 carboxylate, such as the acetate, by addition of corresponding organic sulfonic acid to the solution of the said carboxylate, as follows:

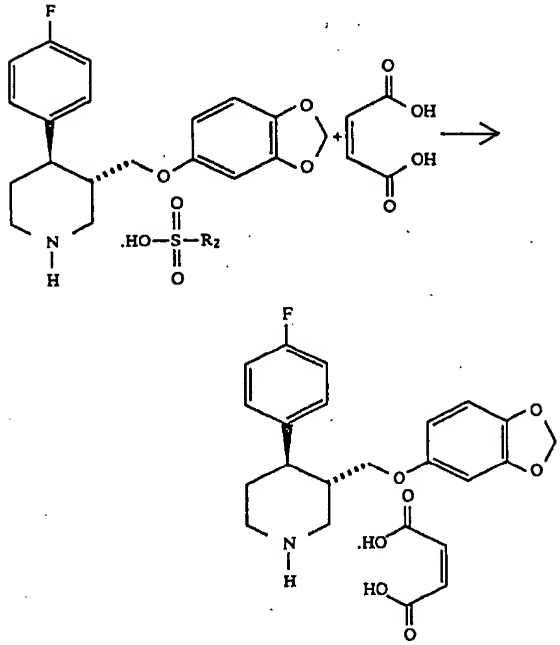


According to a third aspect of the present invention, there is provided a compound obtainable by this process.

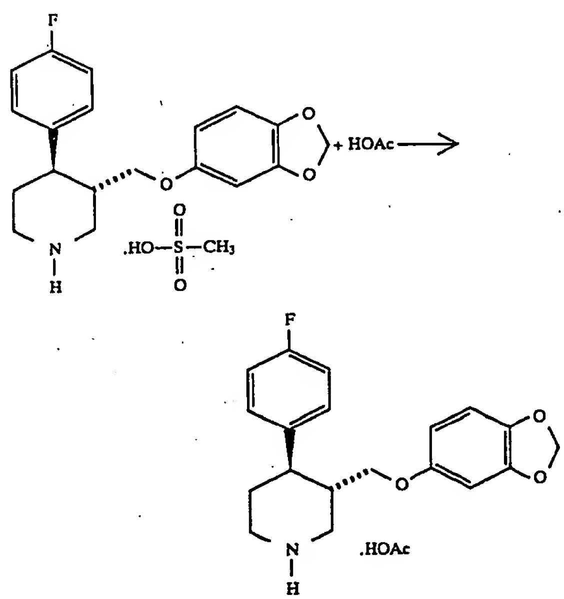
According to a fourth aspect of the present invention there is provided the above compound for use as a medicament and, according to a fifth aspect, a medicament comprising this compound, and to the use thereof for treating depressions, obsessive compulsive disorders, panic disorders, bulimia, anorexia, pain, obesity, senile demential, migraine, anorexia, social phobia, depressions arising from pre-menstrual tension.

According to a sixth aspect of the present invention, there is provided the use of a compound of the invention as a reagent in further syntheses. More specifically, the compounds of the present invention can be used as a start reagent for forming further acid addition salts, for example for

providing further paroxetine acid addition salts, by reacting with a suitable regent, i.e. with a corresponding acid. For example, the formation of paroxetine maleate according to the present invention proceeds by the following equation:

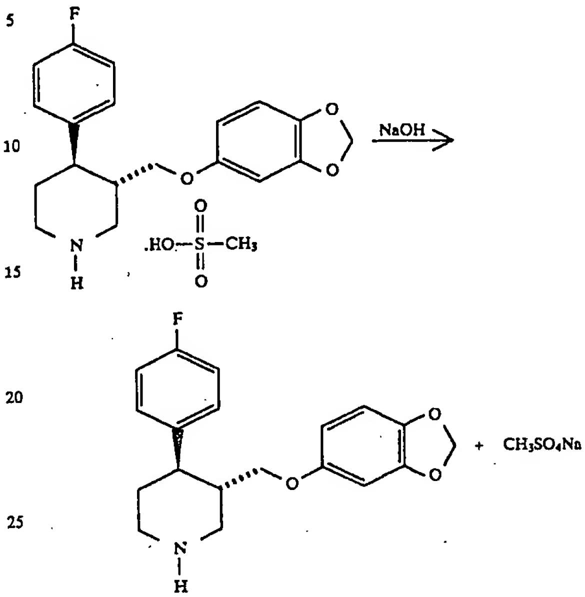


and the formation of paroxetine acetate proceeds as follows:



This is an advantageous route, since by using the substantially pure sulfonic acid salts according to the present invention as a start reagent, the preparation of a further salt, as above, results in this further salt having a high purity. The inventors have shown that such salts have a surprisingly high purity.

Similarly, the compounds of the present invention can react with a base, such as an inorganic and/or an organic base, to form (liberate) free bases of the corresponding compounds. As exemplified on paroxetine, the reaction proceeds according to the equation:



The free bases liberated from the compounds of the present invention have surprisingly higher purity than if prepared by known methods which is especially important in case of their use for production of pharmaceuticals.

Accordingly, the new compounds of the first aspect of the invention can also form hydrates and/or solvates by a contact with a corresponding reaction partner, i.e. with water and/or with a solvent. Examples of such further salts, hydrates and solvates, for example these of paroxetine, are the:

hydrochloride	oxalate	dihydrate
hydrobromide	succinate	trihydrate
hydroiodide	tartrate	hexahydrate
acetate	citrate	methanolate
propionate	embonate	ethanolate
maleate	hemihydrate	
fumarate	hydrate	

The inventors have shown that such salts have a surprisingly high purity.

Examples of bases which can be employed in the preparation of the free bases are: sodium hydroxide, potassium hydroxide, calcium hydroxide, ammonium hydroxide, sodium carbonate, methylamine, dimethylamine, triethylamine, pyridine and such like.

Since the compounds according to the present invention exhibit high solubility, they can be dosed, for example injected, in a high concentration, low volume solution, this method of dosing being particularly advantageous with certain patients, such as manic depressives and such like, i.e. patients who are unable or unwilling to swallow medicine.

The compounds of the present invention can be formulated into various types of pharmaceutical compositions for treatment of humans and animals. Pharmaceutical compositions according to the present invention comprise a compound of the invention alone or together with a pharmaceutically acceptable carrier or diluent. The preferred formulations are those for oral administration (tablets,

capsules) but formulations for parenteral or topical administration are also within the scope of the invention. The high water solubility of the compounds of the invention enables high dissolution rates in solid dosage forms based on the compounds of the invention to be obtained, during the in vitro release as well as good bioavailability after peroral application in vivo.

The tablets containing compounds of the present invention can be prepared both by tabletting procedure in which water is present (e.g. aqueous granulation) as well as by tabletting processing it which water is absent (direct compression, dry granulation) and may be coated by any suitable means of coating.

The present invention will now be further elucidated by way of the following examples and results.

EXPERIMENTAL

A seeding crystal of paroxetine methane sulfonate was made as follows:

2.7 g (8.2 mmol) of paroxetine was dissolved in

15 ml of hot ethanol.

1.0 g (10.4 mmol) of methanesulfonic acid in

15 ml of ethanol was added and the mixture was cooled to room temperature. When the mixture had reached room temperature the mixture was put in the freezer at −20° C. overnight. No crystal line compound was obtained. The mixture was evaporated to dryness leaving an oil. After 1 month at room temperature a waxy solid was obtained. Part of this solid was taken apart and the rest was dissolved in

10 ml of EtOAc. The waxy crystals were added and the mixture was put in the freezer at −20° C. overnight. A white crystalline product was precipitated. After filtration and drying in a vacuumoven

2.5 g (5.9 mmol) of paroxetine methane sulfonate was obtained.

Yield 72%

This seeding crystal was subsequently used in following examples 1 and 3.

EXAMPLES

Example 1

Paroxetine methane sulfonate from paroxetine

To a solution of 43.5 g (132 mmol) of paroxetine, prepared by the procedure disclosed in U.S. Pat. No. 4,007,196, 12.7 g (132 mmol) of methane sulfonic acid was added to

150 ml of boiling ethyl acetate. The mixture was left at room temperature for 2 hours. Subsequently the mixture was placed overnight at −20° C., with a seeding crystal. The obtained solid was filtered off and washed with

50 ml of ether. The obtained white solid was dried overnight in a vacuumoven.

47.1 g (111 mmol) of product

Yield 99.5%

Analytical characterization of the compound obtained is shown in Table 1. The purity of the compound obtained was 98% (HPLC).

Example 2

Paroxetine Benzene Sulfonate From Paroxetine

3.8 g (11.5 mmol) of paroxetine was dissolved in

10 ml of hot ethylacetate.

1.82 g (11.5 mmol) of anhydrous benzenesulfonic acid was added. The mixture was left at room temperature for 2 h. The mixture was evaporated to dryness and dissolved in dichloromethane, and evaporated again to dryness leaving an oil. This oil was solidified through high vacuum (0.1 mmHg) evaporation leaving

5.0 g (1.3 mmol) of an off white solid. To this solid was added

5 ml of acetone and the suspension was stirred for 5 minutes during which a white suspension was obtained. The solid was filtered off and dried under vacuum.

4.8 g (9.9 mmol) of product was obtained.

Yield 85%.

Analytical characterization of the compound obtained is shown in Table 1. The purity of the compound obtained was 99.4% (HPLC).

Example 3

Paroxetine p-toluene Sulfonate From Paroxetine

5.0 g (15 mmol) of paroxetine was dissolved in

25 ml of hot ethylacetate.

2.9 g (15 mmol) of p-toluenesulfonic acid was added. The mixture was left at room temperature for 2 h and subsequently put in the freezer, with a seeding crystal, for 14 h. The solid was filtered off and washed once with

10 ml of n-hexane. The obtained white solid was dried overnight in a vacuumoven.

4.8 g (10 mmol) of a white solid was obtained.

Yield 67%

Analytical characterization of the compound obtained is shown in Table 1. The purity of the compound obtained was 99.4% (HPLC).

Example 4

Paroxetine p-chlorobenzene Sulfonate From Paroxetine

1.1 g (3.3 mmol) of paroxetine was dissolved in

3 ml of hot ethylacetate.

0.76 g (3.3 mmol) of 90% p-chlorobenzenesulfonic acid was added. The mixture was left at room temperature for 1 h and washed with

5 ml of water. The organic layer was dried with Na_2SO_4, filtered and evaporated to dryness leaving

1.5 g (2.9 mmol) of an off white solid.

Yield 88%

Analytical characterization of the compound obtained is shown in Table 1. The purity of the compound obtained was 99.4% (HPLC).

Example 5

Paroxetine Maleate From Paroxetine Methane Sulfonate

1.0 g (2.4 mmol) of paroxetine methane sulfonate in

5 ml of hot water. To this solution was added

0.32 g (2.8 mmol) of maleic acid. The mixture was placed at 4° C. overnight after which a solid with a yellow oil was precipitated on the bottom of the flask. The solid/oil was filtered off and washed 3 times with

10 ml of ether and dried in a vacuumoven.

0.8 g (2.0 mmol) off white crystals were obtained

Yield 85%

The purity of the compound obtained was 99.5% (HPLC).

Example 6

Paroxetine Acetate From Paroxetine Methane Sulfonate

1.0 g (2.4 mmol) of paroxetine methane sulfonate in 5 ml of hot iso-propanol. To this solution was added 0.2 g (3.2 mmol) of acetic acid. The mixture was placed at 4° C. overnight after which a solid was precipitated. The solid was filtered off and washed 3 times with 10 ml of ether and dried in a vacuumoven. 0.5 g (1.3 mmol) off white crystals were obtained

Yield 54%

The purity of the compound obtained was 99.5% (HPLC).

Example 7

Paroxetine free base from paroxetine methane sulfonate

10.0 g (24.0 mmol) of paroxetine methane sulfonate in 150 ml of water and 200 ml of ethyl acetate. To this was added 12.4 g (31 mmol) of an aqueous 10 wt % NaOH solution and the suspension was stirred for 15 minutes. The layers were separated and the aqueous layer was extracted once with 50 ml of ethyl acetate. The combined organic layers are washed once with 100 ml of water and dried over Na_2SO_4. The Na_2SO_4 was filtered off and washed once with 50 ml of ethyl acetate. The ethyl acetate was evaporated off, leaving 7.5 g (22.8 mmol) of an oily product.

Yield 95%

The purity of the compound obtained was 99.5% (HPLC).

A number of the compounds obtained were analysed, the results being shown in tables 1–5 below:

TABLE 1

Characterization of salts of paroxetine with certain organic acids $R\text{-}SO_3H$
R = CH_3 (paroxetine methane sulfonate):
m.p.: 142°–144° C.
DSC curve (closed pan, 10° C./min): onset 145.8° C. 79.0 l/g
IR spectrum (KBr, in cm^{-1}); 531, 546, 777, 838, 931, 962, 1038, 1100, 1169, 1208, 1469, 1500, 1515, 1615, 2577, 2869, 2900, 3023.
1H-NMR (ppm): 1.99 (br d, H_{5eg}, 1H): 2.27 (ddd, H_{5ax}, 1H); 2.48–2.65 (m, H_3, 1H); 2.82–2.92 (m, H_4, CH_3, 4H); 2.95–3.20 (m, H_{2ax}, H_{6ax}, 2H); 3.47 (dd, H_7, 1H); 3.58–3.74 (m, H_{2eg}, H_{6eg}, $H_7$3H): 5.88 (x, H_{7}-2H); 6.10 (dd, $H_{6''}$, 1H); 6.33 (d, $H_{2''}$, 1H): 6.61 (d, $H_{5''}$, 1H); 7.09 (dd, $H_{3'}$, $H_{5'}$, 2H); 7.22 (dd $H_{2'}$, $H_{6'}$, 2H); 8.85 (br d, NH_{eq}, 1H); 9.11 (br d, NH_{ax}, 1H).
13C-NMR (ppm): 30.0 (s, C_5); 39.3 (s, C_3); 39.5 (s, C_4); 41.7 (s, SC); 44.6 (s, C_6); 46.8 (s, C_2); 67.4 (s, C_7): 97.8 (s, $C_{2''}$); 101.2 (s, $C_{7''}$); 105.4 (s, $C_{6''}$); 107.8 (s, $C_{5''}$); 115.8 (d, $C_{3'}$, C_5); 128.4 (s, $C_{6'}$, C_2); 137.1 (s, $C_{4''}$); 142.0 (s, C_1); 148.2 (s, C_3); 153.7 (s, $C_{1''}$); 161.9 (d, $C_{4'}$).
R = C_6H_5 (paroxetine benzene sulfonate):
m.p.: 55°–60° C.
IR spectrum (KBr, in cm31 1): 530, 564, 614, 689, 728, 764, 828, 929, 993, 1007, 1029, 1121, 1179, 1229, 1443, 1471, 1486, 1514, 1600, 1628, 2557, 2842, 3029.
1H-NMR (ppm): 1.90 (br d, H_{5eg}, 1H); 2.10–2.28 (m, H_{5ax}, 1H); 2.38–2.52 (m, H_3, 1H); 2.82 (ddd, H_4, 1H); 3.02–3.18 (m, H_{2ax}, H_{6ax}, 2H); 3.37 (dd, H_7, 1H); 3.48 (d, H_7, 1H); 3.60–3.82 (m, H_{2eg}, H_{6eg}, 2H); 5.87 (s, $H_{7''}$, 2H); 6.06 (dd, $H_{6''}$, 1H); 6.29 (d, $H_{2''}$, 1H); 6.60 (d, $H_{5''}$, 1H); 6.90 (dd, H_3, H_5, 2H); 7.04 (dd, H_2, H_6, 2H); 7.40 (d, ArH, 3H); 7.94 (d, SArH, 2H); 8.81 (br d, NH_{eg}, 1H); 9.04 (br d, NH_{ax}, 1H).
13C-NMR (ppm): 29.9 (s, C_5); 39.2 (s, C_3); 41.5 (s, C_4); 44.8 (s, C_6); 47.0 (s, C_2); 67.3 (s, C_7); 97.9 (s, $C_{2''}$); 101.2 (s, $C_{7''}$); 105.5 (s, $C_{6''}$,) 107.8 (s, $C_{5''}$); 115.7 (d, $C_{3'}$, $C_{5'}$); 125.9 (s, C_b); 128.8 (s, C_d); 128.8 (s, C_6, $C_{2'}$); 130.6 (s, C_{ax}); 137.1 (s, $C_{4''}$); 141.9 (s, C_1); 144.1 (s, C_3); 148.2 (s, $C_{3''}$); 153.7 (s, $C_{1''}$); 161.8 (s, $C_{4'}$).
R = p-$CH_3C_6H_4$ (paroxetine p-toluene sulfonate):
m.p.: 148°–150° C.
DSC curve (closed pan, 10° C./min): onset 151.6° C., 71.6 l/g.
IR spectrum (KBr, in cm^{-1}); 529, 557, 673, 771, 800, 814, 921, 936, 1000, 1029, 1100, 1157, 1136, 1229, 1471, 1486, 1507, 1600, 2557, 2829, 3029.
1H-NMR (ppm): 1.89 (br d, H_{5eg}, 1H); 2.10–2.50 (m, H_{5ax}, H_3, CH_3, 5H); 2.82 (ddd, $H_4$1H); 2.97–3.18 (m, H_{2ax}, H_{6ax}, 2H); 3.36 (dd,$H_7$1H); 3.48 (dd, H_7, 1H); 3.52–3.77 (m, H_{2eg}, H_{6eg}, 2H); 5.87 (s, $H_{7''}$, 2H); 6.06 (dd, $H_{6''}$, 1H); 6.28 (d, $H_{2''}$, 1H); 6.59 (d, $H_{5''}$, 1H); 6.90 (dd, $H_{3'}$, $H_{5'}$, 2H); 7.05 (dd, $H_{2'}$, $H_{6'}$, 2H); 7.24 (d, CH, ArH, 2H); 7.83 (d, SArH, 2H); 8.91 (br d, NH_{eg}, 1H); 9.17 (br d, NH_{ax}, 1H).
13C-NMR (ppm): 21.3 (s, C_6); 29.9 (s, C_5); 39.2 (s, C_3); 41.5 (s, C_4); 44.7 (s, C_6); 46.9 (s, C_2); 67.3 (s, C_7); 97.8 (s, $C_{2''}$); 101.1 (s, $C_{7''}$); 105.5 (s, $C_{6''}$); 107.8 (s, $C_{5''}$); 115.6 (d, C_3, $C_{5'}$); 125.8 (s, C_b); 129.0 (s, C_6, $C_{2'}$); 129.1 (s, C_d); 137.2 (s, C_4-u); 140.8 (s, C_d); 141.5 (s, C_a); 141.9 (s, C_1); 148.2 (s, $C_{3''}$); 153.8 (s, $C_{1''}$); 161.8 (d, $C_{4'}$).
R = p-ClC_6H_4 (paroxetine p-chlorobenzene sulfonate):
m.p.: 75°–80° C.
IR spectrum (KBr, in cm^{-1}): 486, 557, 643, 736, 821, 1000, 1029, 1086, 1114, 1186, 1229, 1471, 1486, 1514, 1600, 1657, 2857, 3029.
1H-NMR (ppm): 1.91 (br d, H_{5eg}, 1H); 2.15 (ddd, H_{5ax}, 1H); 2.37–2.52 (m, H_3, 1H); 2.81 (ddd, H4, 1H); 2.93–3.21 (m, H_{2ax}, H_{6ax}, 2H); 3.37 (dd, H_7, 1H): 3.49 (d, H_7, 1H), 3.61–3.81 (m, H_{2eg}, H_{6eg}, 2H); 5.88 (s, $H_{7''}$, 2H); 6.05 (dd, $H_{6''}$, 1H); 6.27 (d, $H_{2''}$, 1H); 6.59 (d, $H_{5''}$, 1H); 6.91 (dd, H_3, H_5, 2H): 7.03 (dd, H_2, H_6, 2H); 7.39 (d, ClArH, 2H); 7.86 (d, SArH, 2H); 8.78 (br d, NH_{eg}, 1H); 9.02 (br d, NH_{ax}, 1H).
13C-NMR (ppm): 30.0 (s, C_5); 39.3 (s, C_3); 41.5 (s, C_4); 44.9 (s, C_6); 47.1 (s, C_2); 67.3 (s, $C_{7'}$); 97.9 (s, $C_{2''}$); 101.2 (s, $C_{7''}$); 105.5 (s, $C_{6''}$); 107.9 (s, $C_{5''}$); 115.8 (d, C_3, $C_{5'}$); 127.6 (s, C_b); 128.8 (s, C_6, $C_{2'}$); 132.0 (s, C_d); 137.0 (s, C_6); 137.2 (s, $C_{4''}$); 141.8 (s, $C_{1'}$); 142.0 (s, $C_{6'}$); 148.2 (s, $C_{3''}$); 153.6 (s, $C_{1''}$); 161.8 (d, $C_{4'}$).

The compounds of the invention are crystalline, with defined melting points, DSC curves and IR spectra. It cannot be excluded that, under different conditions of their formation and under specific conditions, they could exist also in other crystalline or polymorph modifications which may differ from those as described herein. The compounds of the invention are also generally very stable and non-hygroscopic.

It should be understood that the present invention comprising acid addition salts with organic sulfonic acids are substantially free of the bound organic solvent. Preferably, the amount of bound organic solvent should be less than 2.0% (w/w) as calculated on the anhydrous basis. They nevertheless may contain crystallization water and also unbound water, that is to say water which is other than water of crystallization.

In the following tables 2 and 3, examples of results of hygroscopicity tests and stability tests (in comparison with known salts of paroxetine) are presented.

TABLE 2

Hygroscopicity of certain salts of paroxetine (40° C., 75% rel. hum).

water content (in %) at	t = 0	1 = 4 weeks
methane sulfonate	0.35	+0.04
p-toluene sulfonate	0.70	<0.02
hydrochloride	—	+2.5

TABLE 3

Solubility of paroxetine salts in water (in mg/ml)		
	20° C.	50° C.
methane sulfonate	>1000	1300
p-toluene sulfonate	>1000	>1000
hydrochloride hemidhydrate	4.9	12.6
hydrochloride anhydrate	8.2	24.2

TABLE 4

Stability of paroxetine salts by HPLC (total amount of degradation in %).		
	degradation 20° C.	80° C.
methane sulfonate	not observed	<0.2%, 3 months
p-toluene sulfonate	not observed	<0.2%, 3 months
maleate	0.2%, 12 months	>50%, 5 days

TABLE 5

Solubility of slats of paroxetine in nonaqueous solvents (in mg/ml)			
		methane sulfonate	p-toluene sulfonate
Ethanol	20° C.	36	50
	78° C.	250	>500
2-Propanol	20° C.	7	14
	82° C.	330	>500
Acetone	20° C.	5	16
	56° C.	37	125
Ethyl acetate	20° C.	2	22
	77° C.	25	>500
n-Hexane	20° C.	<0.05	<0.05
	69° C.	0.05	<0.05

Examples of analytical data of the paroxetine salts and the free base prepared in Examples 5 to 7 are given in Table 6.

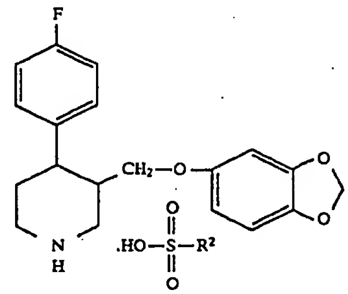
TABLE 6

Characterization of salts/free base of praoxetine
paroxetine maleate:
m.p.: 128–130° C. 1H-NMR (ppm); 1.65–2.00 (m, H_{5eg}, 2H); 2.00–2.50 (m, H_3, 1H); 2.55–3.15 (m, H_{2ax}, H_{6ax}, H_4, 3H); 3.15–3.75 (m, H_{2eg}, H_{6eg}, H_7 3H); 5.67 (s, H7, 2H); 5.97 (s, H_a, 1H); 6.12 (dd, $H_{6''}$, 1H); 6.42 (d, $H_{2''}$, 1H) 6.67 (d, $H_{5''}$, 1H); 6.95–7.35 (m, $H_{2'}$, $H_{3'}$, $H_{5'}$, $H_{6'}$, 4H).
paroxetine acetate:
m.p.; 123–125° C. 1H-NMR (ppm); 1.70–2.00 (m, H_{5eg}, H_{5ax}, 2H); 1.97 (s, H_a, 3H); 2.05–2.50 (m, H_3, 1H); 2.50–3.00 (m, H_4, H_{2ax}, H_{6ax}, 3H); 3.05–3.75 (m, H_{2eg}, H_{6eg}, H_7, 3H); 6.05 (s, $H_{7''}$, 2H); 6.28 (dd, $H_{6''}$, 1H); 6.58 (d, $H_{2''}$, 1H); 6.65 (d, $H_{5''}$, 1H); 7.10–7.50 (m, $H_{2'}$, $H_{3'}$, $H_{5'}$, $H_{6'}$, 4H).
paroxetine:
1H-NMR (ppm): 1.60–2.00 (m, H_{ax}, H_{5eg}, 2H); 2.00–2.35 (m, H_3, 1H); 2.40–2.95 (m, H_4, H_{2ax}, 3H); 3.15–3.70 (m, H_{2eg}, H_{6eg}, H_7, 2H); 5.67 (s, H_7, 2H); 6.11 (dd, $H_{6''}$, 1H); 6.43 (d, $H_{2''}$, 1H); 6.62 (d, $H_{5''}$, 1H); 6.80–7.35 (m, $H_{2'}$, $H_{3'}$, $H_{5'}$, $H_{6'}$, 4H).

It will be clear that the invention is not limited to the above description, but is rather determined by the following claims.

We claim:

1. A compound having the formula:



wherein R^2 represents C_1–C_{10} alkyl group or a substituted or unsubstituted phenyl group wherein the substituents are selected from the group consisting of C_1–C_{10} alkyl, halogen, nitro, hydroxy, alkoxy, and combinations thereof.

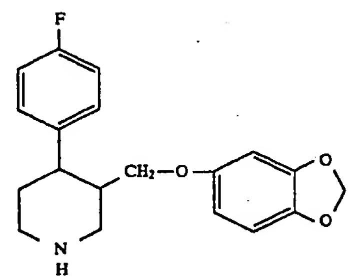
2. The compound according to claim 1, wherein the R^2 group represents a C_1–C_4 alkyl group.

3. The compound according to claim 1, wherein the R^2 group is a C_1–C_2 alkyl group.

4. The compound according to claim 1, having a solubility at about 20° C. of at least about 10 mg per ml water.

5. The compound according to claim 4, having a solubility in water of at least 1000 mg per ml at about 20° C.

6. A process, which comprises mixing together a compound, a salt, and/or a base thereof, having the formula:



with a sulfonic acid of the general formula R^2-SO_3H, wherein

R^2 represents C_1–C_{10} alkyl group or a substituted or unsubstituted phenyl group wherein the substituents are selected from the group consisting of C_1–C_{10} alkyl, halogen, nitro, hydroxy, alkoxy, and combinations thereof,

to produce a sulfonate salt compound according to claim 1.

7. The process according to claim 6, which further comprises mixing together said sulfonate salt compound with a reagent selected from the group consisting of hydrochloric acid, hydrobromic acid, hydriodic acid, acetic acid, propionic acid, maleic acid, fumaric acid, oxalic acid, succinic acid, tartaric acid, citric acid, embonic acid/pamoic acid, sulfuric acid, water, methanol, and ethanol, to form a salt or solvate of said reagent.

8. The process according to claim 7, wherein the salt of said reagent is produced and is recovered as a solid having a purity of at least 90 wt %.

9. The process according to claim 7, wherein said reagent is maleic acid; said mixing produces paroxetine maleate; and which further comprises recovering said paroxetine maleate in a purity of at least 98%.

10. The process according to claim 7, wherein said reagent is acetic acid; said mixing produces paroxetine acetate; and which further comprises recovering said paroxetine acetate in a purity of at least 98%.

11. A process according to claim 6, which further comprises mixing together said sulfonate salt compound with at least one of an organic or an inorganic base to form a free base thereof.

12. The process according to claim 11, wherein the base is selected from the group consisting essentially of: sodium hydroxide, potassium hydroxide, calcium hydroxide, ammonium hydroxide, sodium carbonate, methylamine, dimethylamine, triethylamine, and pyridine.

13. The process according to claim 11, further comprising isolating said free base in a purity of at least 95%.

14. The process according to claim 13, wherein said isolated free base has a purity of at least 98%.

15. The compound produced by the process according to claim 6.

16. A pharmaceutical composition comprising a therapeutically effective amount of a compound according to claim 1 and at least one pharmaceutically acceptable carrier or diluent.

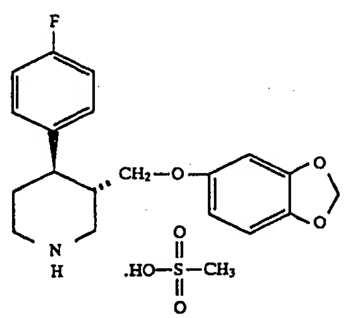
17. The pharmaceutical composition according to claim 16, wherein said composition is a solid dosage form.

18. A method for treating depression, obsessive/compulsive disorders, panic disorders, bulimia, anorexia, pain, obesity, senile dementia, migraine, or social phobias, which comprises administering to a patient in need thereof a therapeutically effective amount of the compound as claimed in claim 1.

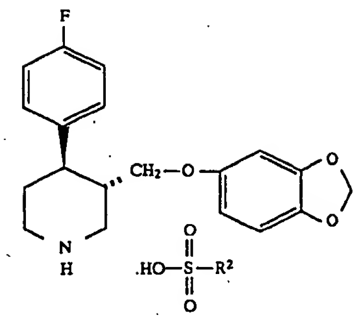
19. The method according to claim 18, wherein said patient is a human.

20. The method according to claim 18, wherein said method comprises administering an effective antidepressant amount of said compound to a patient suffering from depression.

21. A compound of the following formula:



22. A pharmaceutical composition comprising a therapeutically effective amount of a compound of the following formula:



wherein R^2 is methyl, ethyl, benzyl, p-chlorobenzyl, or tolyl; and

a pharmaceutically acceptable carrier or diluent.

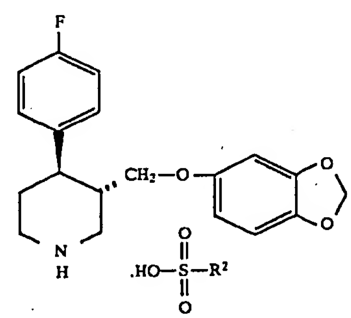
23. The pharmaceutical composition according to claim 22, wherein said composition is for oral administration.

24. The pharmaceutical composition according to claim 22, wherein R^2 is methyl.

25. The pharmaceutical composition according to claim 24, wherein said composition is a solid dosage form.

26. The pharmaceutical composition according to claim 25, wherein said composition is a tablet.

27. A method of treating depression, obsessive/compulsive disorders or panic disorders which comprises administering to a patient in need thereof an effective amount of a compound of the following formula:



wherein R^2 is methyl, ethyl, benzyl, p-chlorobenzyl, or tolyl.

28. The method according to claim 27, wherein R^2 is methyl.

29. The method according to claim 28, wherein an effective antidepressant amount is administered to said patient.

* * * * *

US005208232A

United States Patent [19]

Jakobsen et al.

[11] Patent Number: 5,208,232

[45] Date of Patent: May 4, 1993

[54] PIPERIDINE COMPOUNDS AND THEIR PREPARATION AND USE

[75] Inventors: Palle Jakobsen; Jørgen Dreger, both of Vaerløse, Denmark

[73] Assignee: Novo Nordisk A/S, Måløv, Denmark

[21] Appl. No.: 673,729

[22] Filed: Mar. 22, 1991

Related U.S. Application Data

[60] Division of Ser. No. 337,301, Apr. 13, 1989, Pat. No. 5,017,585, which is a continuation-in-part of Ser. No. 106,154, Oct. 8, 1987, Pat. No. 4,877,799.

[30] **Foreign Application Priority Data**

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Jun. 25, 1987	[DK]	Denmark	3234/87
Apr. 28, 1988	[DK]	Denmark	2310/88

[51] Int. Cl.^{5} C07D 417/06; C07D 413/06; A61K 31/535; A61K 31/54

[52] U.S. Cl. 514/228.2; 514/227.8; 514/233.8; 514/235.5; 514/316; 514/321; 514/326; 544/60; 544/62; 544/129; 546/193; 546/157; 546/207; 546/214

[58] Field of Search 544/60, 129, 62; 546/193, 197, 207, 214; 514/227.8, 235.5, 228.2, 316, 321, 326, 233.8

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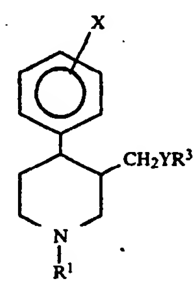
Primary Examiner—C. Warren Ivy
Assistant Examiner—Celia Chang
Attorney, Agent, or Firm—Gordon W. Hueschen

[57] **ABSTRACT**

Novel piperidine compounds having the formula



(I)

wherein the symbols have the same meanings as set forth in the specification, and salts thereof with a pharmaceutically acceptable acid, are disclosed.

The novel compounds are useful in the treatment of anoxia, migraine, ischemia and epilepsy.

10 Claims, No Drawings

PIPERIDINE COMPOUNDS AND THEIR PREPARATION AND USE

The present application is a division of our prior-filed copening application, Ser. No. 337,301, filed Apr. 13, 1989, now U.S. Pat. No. 5,017,585, issued May 21, 1991, which in turn is a continuation-in-part of Ser. No. 106,154, filed Oct. 8, 1987, now U.S. Pat. No. 4,877,799, issued Oct. 31, 1989.

The present invention relates to therapeutically active piperidine compounds, a method of preparing the same and to pharmaceutical compositions comprising the compounds. The novel compounds are useful in the treatment of anoxia, ischemia, migraine and epilepsy.

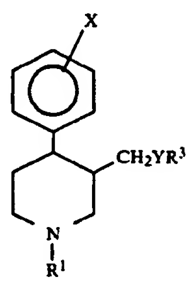
It is well known that accumulation of calcium in the brain cells (calcium overload) is seen after periods of uncontrolled hyperactivity in the brain, such as after convulsions, migraine, anoxia and ischemia. As the concentration of calcium in the cells is of vital importance for the regulation of cell function, an uncontrolled high concentration of the cell calcium will lead to, or indirectly cause the symptoms and possibly also the degenerative changes combined with the above diseases.

Therefore calcium overload blockers selective for brain cells will be useful in the treatment of anoxia, ischemia, migraine and epilepsy.

Well known calcium antagonists such as nifedipine, verapamil and diltiazem have activity against pheripheral calcium uptake, e.g. in blood vessels and the heart, however have shown only very low activity against calcium overload in brain cells.

Accordingly it is an object of the invention to provide novel compounds having activity against calcium overload in brain cells.

The novel compounds of the invention are piperidine compounds having the general formula I



(I)

wherein

R^3 is 3,4-methylenedioxyphenyl, aryl or heteroaryl which are optionally substituted with one or more halogen, C_{1-6}-alkoxy, optionally substituted aryloxy or aryl-C_{1-6}-alkoxy, cyano, mono or poly halogenated C_{1-6}-alkyl, C_{1-6}-alkenyl, C_{1-6}-alkyl, C_{3-5}-alkylene or trifluoromethyl groups,

R^1 is straight or branched C_{1-8}-alkyl unsubstituted or substituted with one or more cyano, ester, dialkylamino, hydroxy, amido, halogeno, substituted or unsubstituted piperidino, morpholino, thiomorpholino, dioxolanyl, tetrahydrofuranyl, C_{1-8}-alkoxy or C_{3-8} cycloalkyl groups,

X is hydrogen, halogen, trifluoromethyl, hydroxy, cyano or C_{1-8}-alkoxy,

Y is O or S;

provided that R^1 is not unsubstituted C_{1-8}-alkyl, C_{1-6}-alkoxy-C_{1-8}-alkyl or C_{3-8}-cycloalkyl-C_{1-8}-alkyl, when R^3 is 3,4-methylenedioxyphenyl, aryl or heteroaryl optionally substituted with one or more C_{1-6}-alkyl, C_{1-6}-alkoxy, C_{3-5}-alkylene, C_{3-8}-cycloalkyl or aralkoxy, and at the same time X is hydrogen or halogen

and salts thereof with a pharmaceutically acceptable acid.

Preferred compounds of formula I are compounds wherein,

R^3 is 3,4-methylenedioxyphenyl, optionally substituted with halogen or C_{1-6}-alkoxy or phenyl substituted with C_{3-5}-alkylene, and/or R^1 is straight or branched C_{1-8}-alkyl, and/or X is hydrogen, halogen, trifluoromethyl or C_{1-6}-alkoxy.

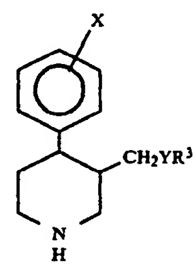
Aryl is intended to mean carbocylic aromatic rings, preferably phenyl.

Heteroaryl is intended to mean mono or fused dicyclic rings of up to 12 carbon atoms including one or more heteroatoms.

Examples of such salts include inorganic and organic acid addition salts such as hydrochloride, hydrobromide, sulphate, phosphate, acetate, fumarate, maleate, citrate, lactate, tartrate, oxalate, or similar pharmaceutically-acceptable inorganic or organic acid addition salts.

The invention also relates to a method of preparing the above mentioned compounds. These methods comprise

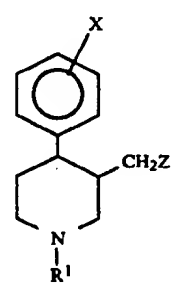
a) reacting a compound having the general formula II



(II)

wherein R^3, X and Y have the meanings defined above, with a compound having the the general formula R^1-Z, wherein Z is a leaving group such as halogen and R^1 has the meaning defined above, or

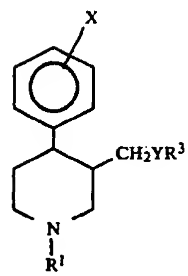
b) reacting a compound having the general formula III



(III)

wherein R^1 and X have the meanings defined above, and Z is a leaving group, with a compound having the the general formula R^3-YH, wherein Y is O or S and R^3 has the meaning defined above, or

c) reacting a compound having the general formula I,



(I)

wherein X, R^1, R^3 and Y have the meanings defined above, with bromine, and optionally thereafter forming a salt with a pharmaceutically acceptable acid.

The pharmacological properties of the compounds of the invention can be illustrated by determining their capability to inhibit calcium uptake into brain synaptosomes.

PRINCIPLE

Depolarization of neuronal membranes leads to an opening of so-called 'voltage operated calcium channels' (VOC) in the membranes which allows a massive influx of calcium from the extracellular space. A crude synaptosomal preparation (so-called P_2 fraction) contains small vesicles surrounded by neuronal membrane and it is possible in such a preparation to study a depolarization-induced opening of VOC. In the present model ^{45}Ca influx is induced in the synaptosomes by depolarization with elevated potassium concentrations, and the effect of test substances on this stimulated uptake is studied (Nachshen, D. A. and Blaustein, M. P., Mol. Pharmcol., 16, 579 (1979)).

ASSAY

A male Wistar rate is decapitated and the cerebral cortex removed and homogenized in 10 ml of ice-cold 0.32M sucrose using a glass homogenizer with a teflon pestle. All subsequent steps for isolation of synaptosomes are done at 0°–4° C. The homogenate is centrifuged at 1000×g for 10 min and the resulting supernatant is re-centrifuged at 18000×g for 20 min. This pellet (P_2) is resuspended in 0.32M sucrose (5 ml per g of original tissue) with a teflon pestle.

Aliquots (0.050 ml) of this crude synaptosomal suspension are added to glass tubes containing 0.625 ml of NaCl buffer (136 mM NaCl, 4 mM KCl, 0.35 mM $CaCl_2$, 1.2 mM $MgCl_2$, 20 mM Tris HCl, 12 mM glucose, pH 7.4) and 0.025 ml of various drug solutions in 48% Ethanol. The tubes are pre-incubated for 30 min on ice and then for 6 min at 37° C. in a water bath.

The uptake is immediately initiated by adding 0.4 ml of $^{45}CaCl_2$(specific activity=29–39 Ci/g; 0.5 Ci/assay), in 145 mM NaCl for non-depolarized samples and in 145 mM KCl for depolarized samples. The incubation is continued for 15 s.

The uptake is terminated by rapid filtration through GF-C glass fiber filters which are washed three times with 5 ml of a cold solution containing 145 mM KCl, 7 mM EGTA and 20 mM Tris HCl, pH 7.4. The amount of radioactivity on the filter disc is determined by liquid scintillation spectrometry.

TEST PROCEDURE

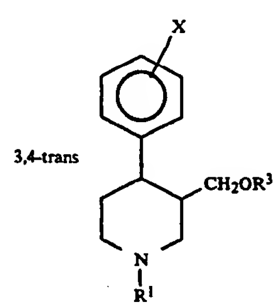
Test substances are dissolved in 10 ml of 48% ethanol at a concentration of 0.44 mg/ml. Dilution are made in 48% ethanol. Experiments are performed in quadruplicate. Controls for depolarized and nondepolarized samples are included in the assay and test substances are only tested in depolarized samples.

RESULTS

Test values are given as MEC (minimal effective concentration, µg/ml), which inhibit stimulated uptake of ^{45}Ca significant different ($P<0.05$, Student's t-test) from control.

Test results obtained by testing some compounds of the present invention are given in the following table 1.

TABLE I



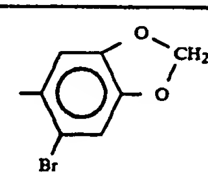
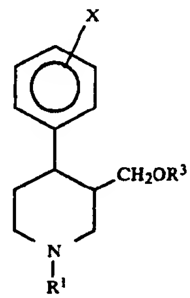
R^1	R^3	X	OPTIC FORM	MEC µg/ml
$-(CH_2)_3CH_3$		4-F	(−)	0.3

TABLE I-continued

3,4-trans



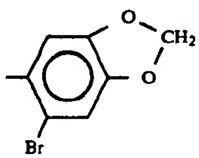
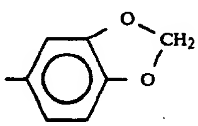
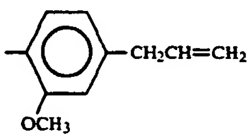
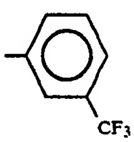
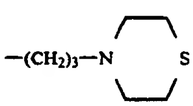
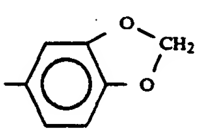
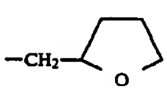
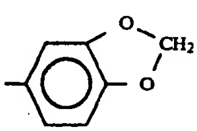
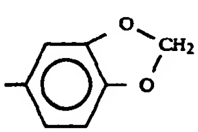
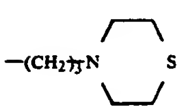
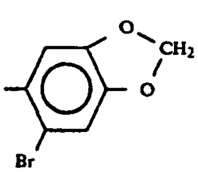
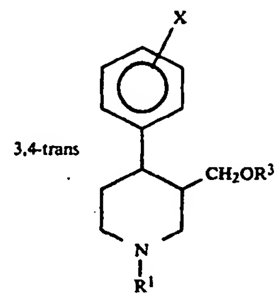
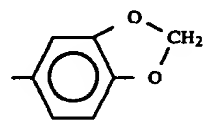
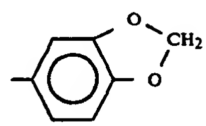
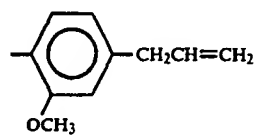
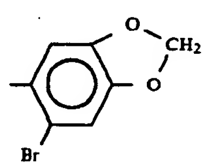
R^1	R^3	X	OPTIC FORM	MEC μg/ml
$-(CH_2)_4CH_3$		H	(−)	0.3
$-(CH_2)_4CH_3$		4-OCH_3	(+−)	1
$-CH_3$		H	(+−)	1
$(CH_2)_4CH_3$		H	(+−)	1
		4-F	(−)	0.3
		—	(−)	1
$-CH_3$		3-CF_3	(+−)	1
		4-F	(−)	1

TABLE I-continued



R^1	R^3	X	OPTIC FORM	MEC µg/ml
$-(CH_2)_4CH_3$		$3-CF_3$	(+−)	0.3
$-(CH_2)_4CH_3$		$4-O(CH_2)_4CH_3$	(+−)	0.3
$-(CH_2)_3CH_3$		H	(+−)	0.3
$-(CH_2)_4CH_3$		4-F	(+)	0.3

The compounds of the invention, together with a conventional adjuvant, carrier, or diluent, and if desired in the form of a pharmaceutically-acceptable acid addition salt thereof, may be placed into the form of pharmaceutical compositions and unit dosages thereof. In such forms they may be employed as solids, such as tablets or filled capsules, or liquids, such as solutions, suspensions, emulsions, elixirs, or capsules filled with the same, all for oral use; in the form of suppositories for rectal administration; or in the form of sterile injectable solutions for parenteral (including subcutaneous) use. Such pharmaceutical compositions and unit dosage forms thereof may comprise conventional ingredients in conventional proportions, with or without additional active compounds or principles, and such unit dosage forms may contain any suitable effective calcium overload blocking amount of the active ingredient commensurate with the intended daily dosage range to be employed. Tablets containing ten (10) milligrams of active ingredient or, more broadly, ten (10) to hundred (100) milligrams, per tablet, are accordingly suitable representative unit dosage forms.

The compounds of this invention can thus be used for the formulation of pharmaceutical preparations, e.g. for oral and parenteral administration to mammals including humans, in accordance with conventional methods of galenic pharmacy.

Conventional excipients are such pharmaceutically acceptable organic or inorganic carrier substances suitable for parenteral or enteral application which do not deleteriously react with the active compounds.

Examples of such carriers are water, salt solutions, alcohols, polyethylene glycols, polyhydroxyethoxylated castor oil, gelatine, lactose, amylose, magnesium stearate, talc, silicic acid, fatty acid monoglycerides and diglycerides, pentaerythritol fatty acid esters, hydroxymethylcellulose and polyvinylpyrrolidone.

The pharmaceutical preparations can be sterilized and mixed, if desired, with auxiliary agents, emulsifiers, salt for influencing osmotic pressure, buffers and/or coloring substances and the like, which do not deleteriously react with the active compounds.

For parenteral application, particularly suitable are injectable solutions or suspensions, preferably aqueous solutions with the active compound dissolved in polyhydroxylated castor oil.

Ampoules are convenient unit dosage forms.

Tablets, dragees, or capsules having talc and/or a carbohydrate carrier or binder or the like, the carrier preferably being lactose and/or corn starch and/or potato starch, are particularly suitable for oral applica-

tion. A syrup, elixir or the like can be used in cases where a sweetened vehicle can be employed.

Generally, the compounds of this invention are dispensed in unit form comprising 0.05–100 mg in a pharmaceutically acceptable carrier per unit dosage.

The dosage of the compounds according to this invention is 0.1–300 mg/day, preferably 10–100 mg/day, when administered to patients, e.g. humans, as a drug.

A typical tablet which may be prepared by conventional tabletting techniques contains:

Active compound	5.0 mg
Lactosum	67.8 mg Ph.Eur.
Avicel ™	31.4 mg
Amberlite ™ IRP 88	1.0 mg
Magnesii stearas	0.25 mg Ph.Eur.

Due to the high calcium overload blocking activity, the compounds of the invention are extremely useful in the treatment symptoms related to an accumulation of calcium in brain cells of mammals, when administered in an amount effective for blocking calcium overload in brain cells. The important calcium overload blocking activity of compounds of the invention includes both activity against anoxia, ischemia, migraine and epilepsy. The compounds of the invention may accordingly be administered to a subject, e.g., a living animal body, including a human, in need of a calcium overload blocker, and if desired in the form of a pharmaceutically-acceptable acid addition salt thereof (such as the hydrobromide, hydrochloride, or sulfate, in any event prepared in the usual or conventional manner, e.g., evaporation to dryness of the free base in solution together with the acid), ordinarily concurrently, simultaneously, or together with a pharmaceutically-acceptable carrier or diluent, especially and preferably in the form of a pharmaceutical composition thereof, whether by oral, rectal, or parenteral (including subcutaneous) route, in an effective calcium overload blocking amount, and in any event an amount which is effective for the treatment of anoxia, ischemia, migraine or epilepsy, traumatic head injury and neurodegerative diseases due to their calcium overload blocking activity. Suitable dosage ranges are 1–200 milligrams daily, 10–100 milligrams daily, and especially 30–70 milligrams daily, depending as usual upon the exact mode of administration, form in which administered, the indication toward which the administration is directed, the subject involved and the body weight of the subject involved, and the preference and experience of the physician or veterinarian in charge.

The invention will now be described in further detail with reference to the following examples:

EXAMPLE 1

(−)-trans-1-(2-cyanoethyl)-4-(4-fluorophenyl)-3-(3,4-methylenedioxyphenoxymethyl)-piperidine hydrochloride

1 g of (−)-trans-4-(4-fluorophenyl)-3-(3,4-methylene dioxyphenoxymethyl)-piperidine hydrochloride in 50 ml 99.9% ethanol was mixed with 3-bromopropionitrile (7 ml) and 2 g potassium carbonate. The mixture was refluxed for 70 h. After cooling 25 ml acetone and 25 ml diethylether were added, the precipitate filtered off, and the filtrate evaporated in vacuo. The residue was extracted with 1N NaOH/ether, the ether layer dried ($MgSO_4$) and evaporated to dryness. The residue was dissolved in acetone and excess conc. HCl was added. Subsequent evaporation gave a hard glass, which was purified on a silica gel column using 99.5% ethanol as eluent. The title compound was isolated, and its structure confirmed by the IR and NMR data. M.p. 156° C.

The following compounds were prepared in the same manner from (−)-trans-4-(4-fluorophenyl)-3-(3,4-methylenedioxyphenoxymethyl)piperidine hydrochloride and the relevant halogeno compound (the actual halogen given). Oxalates were prepared from the free base by mixing aquimolar amounts of amine and oxalic acid (anhydrous) in acetone solution, which caused precipitation of the oxalate after few min at RT or in the fridge:

(−)-trans-1-(3-(4,4-dimethyl-1-piperidyl)-propyl)-4-(4-fluorophenyl)-3-(3,4-methylenedioxyphenoxymethyl)-piperidine dihydrochloride, from equimolar amounts of the "piperidine" and the chloro compound. Reflux time 190 h, m.p. 267° C.

(−)-trans-1-(3-dimethylaminopropyl)-4-(4-fluorophenyl)-3-(3,4-methylenedioxyphenoxymethyl)-piperidine dihydrochloride, from the chloro compound by reflux for 50 h, a few crystals of iodine added. M.p. 295° C.

(−)-trans-4-(4-fluorophenyl)-3-(3,4-methylenedioxyphenoxymethyl)-1-(3-(2-methyl-1-piperidyl)propyl)-piperidine dihydrochloride, from equimolar amounts of "piperidine" and the chloro compound by reflux for 3 h, a few crystals of I_2 added. M.p. 250° C.

(−)-trans-1-(2-ethoxycarbonylethyl)-4-(4-fluorophenyl)-3-(3,4-methylene dioxyphenoxymethyl)piperidine oxalate, from the bromo compound, reflux time 2 h, m.p. 51° C., purified by column chromatography on silicagel using CH_2Cl_2/CH_2OH 9:1 as eluent.

(−)-trans-4-(4-fluorophenyl)-3-(3,4-methylenedioxyphenoxymethyl)-1-(3-thiomorpholinylpropyl)-piperidine dihydrochloride, from equimolar amounts of "piperidine" and the chloro compound, a few crystals I_2 added, reflux time 3 h, m.p. 267° C.

(−)-trans-1-carbamoylmethyl-4-(4-fluorophenyl)-3-(3,4-methylenedioxyphenoxymethyl)-piperidine hydrochloride, from the iodo compound, reflux for 2 h, m.p. 104° C.

(−)-trans-4-(4-fluorophenyl)-3-(3,4-methylenedioxyphenoxymethyl)-1-(3-morpholinopropyl)-piperidine dihydrochloride, from equimolar amounts of "piperidine" and the chloro compound, a few crystals of iodine added, reflux for 30 h, m.p. 108° C.

(−)-trans-1-(4-cyanobutyl)-4-(4-fluorophenyl)-3-(3,4-methylenedioxyphenoxymethyl)-piperidine oxalate, from the bromo compound by addition of a few iodine crystals, and reflux for 1 h. The free bases was purified on a silicagel column using CH_2Cl_2/CH_3OH 9:1 as eluent, m.p. 89° C.

(−)-trans-1-(1,3-dioxolyl-2-methyl)-4-(4-fluorophenyl)-3-(3,4-methylenedioxyphenoxymethyl)-piperidine oxalate, from the bromo compound, addition of one iodine crystal, reflux for 120 h, m.p. 53° C.

(−)-trans-4-(4-fluorophenyl)-1-tetrahydrofurfuryl-3-(3,4-methylenedioxyphenoxymethyl)-piperidine oxalate, from the bromo compound, reflux time 7 h, purified on silicagel column, eluent CH_2Cl_2/CH_3OH 9:1, hard glass. Identified by NMR and MS data. MS (m/e, % of base peak): 413,5; 343,38; 342,100; 204,25; 137,28; 109,38; 83,42; 58,100; 57,55.

(−)-trans-4-(4-fluorophenyl)-1-(6-hydroxyhexyl)-3-(3,4-methylenedioxyphenoxymethyl)-piperidine oxalate, from the chloro compound, addition of a few crys-

tals of iodine, reflux for 24 h, purified by column chromatography on silicagel CH_2Cl_2/CH_3OH 9:1 as eluent hard glass. Identified by IR, NMR and MS-data. MS (m/e, % og base peak): 429,3; 343,15; 342,55; 204,10; 171,10; 137,12; 109,15; 58,100.

(−)-trans-4-(4-fluorophenyl)-1-(3-hydroxypropyl)-3-(3,4-methylenedioxyphenoxymethyl)-piperidine oxalate, from the bromo compound, reflux 7 h, isolated as a hard glass, identified by IR and NMR.

EXAMPLE 2

(+−)-trans-1-methyl-3-(6-bromo-2-naphthoxymethyl)-4-phenylpiperidine hydrochloride

6-bromo-2-naphthol (2.45 g) was dissolved in MIBC (40 ml). NaOH (0.52 g) was added, and the mixture was stirred for ½ h. (+−)-trans-1-methyl-4-phenyl-3-phenyl-sulfonyloxymethylpiperidine (3.5 g) dissolved in MIBC (50 ml) was added to the "phenolate" solution, heating to 110° C. for 6 h. The reaction mixture was evaporated to dryness and the residue extracted with OH/ether. The ether layer was dried (Na_2SO_4) filtered and evaporated to dryness. The crude product was purified on silicagel, petrolether/CH_3OH 1:1 as eluent. The purified product was dissolved in ether and precipitated with excess conc. HCl-solution. Reprecipitation from acetone/ether gave 0.7 g compound, m.p.225° C.

In the same manner were prepared the following compounds from (+−)-trans-1-methyl-4-phenyl-3-phenylsulfonyloxymethylpiperidine and the appropriate substituted phenol or naphthol. Oxalates were prepared by mixing equimolar amounts of "piperidine base" and anhydrous oxalic acid in acetone solution.

(+−)-trans-1-methyl-3-(3-trifluoromethylphenoxymethyl-4-phenylpiperidine oxalate. Heating at 130° C. until the sulfoester had reacted as seen by TLC. M.p. 92° C.

(+−)-trans-3-(4-chloro-1-naphthoxymethyl)-1-methyl-4-phenylpiperidine oxalate. Heating to 110° C. for 14 h. M.p. 88° C.

(+−)-
-trans-3-(4-allyl-2-methoxyphenoxymethyl)-4-phenyl-piperidine oxalate. Reaction time 40 h at 110° C. M.p. 137° C.

(+−)-trans-1-methyl-3-(3-phenoxyphenoxymethyl)-4-phenylpiperidine oxalate. M.p. 166° C.

(+−)-trans-3-(2-cyanophenoxymethyl)-1-methyl-4-phenylpiperidine oxalate. M.p. 108°-110° C.

EXAMPLE 3

(+−)-trans-3-(3-trifluoromethylphenoxymethyl)-4-phenylpiperidine hydrochloride was prepared by means of alpha-chloroethyl chloroformate using the method described in J. Org. Chem. 49 (1984) 2081 (R. A. Olofson, J. T. Martz, J. P. Senel, M. Piteau and T. Malfroot). Na-dried toluene was used as solvent instead of 1,2-dichloroethane in the primary reaction. M.p. 171° C.

The following compounds were prepared in exactly the same manner by N-dealkylation of the corresponding N-methyl compound.

(+−)-trans-4-(4-methoxyphenyl)-3-(3,4-methylenedioxyphenoxymethyl)-piperidine. The hydrochloride was extracted with NaOH/ether, the above mentioned compound was precipitated from acetone/ether, m.p. 184° C.

(+−)-trans-3-(4-allyl-2-methoxyphenoxymethyl)-4-phenylpiperidine oxalate. The hydrochloride was extracted with OH^-/ether, the ether phase evaporated to dryness, and the residue dissolved in acetone and precipitated with an equimolar amount of anhydrous oxalic acid in acetone solution, m.p. 101° C.

(+−)-trans-3-(3-phenoxyphenoxymethyl)-4-phenylpiperidine oxalate. The hydrochloride was extracted with OH^-/ether, the ether phase evaporated to dryness, and the residue dissolved in acetone and precipitated by means of an equimolar amount of anhydrous oxalic acid in acetone solution. M.p. 138°-142° C.

EXAMPLE 4

The following compounds were prepared using the alkylation method described in example 1.

(+−)-trans-3-(3-trifluoromethylphenoxymethyl)-1-pentyl-4-phenylpiperidine oxalate, from (+−)-trans-3-(3-trifluoromethylphenoxymethyl)-4-phenylpiperidine and pentyl bromide by reflux for 10 h. M.p. 130° C.

(+−)-trans-4-(4-methoxyphenyl)-3-(3,4-methylenedioxyphenoxymethyl)-1-pentylpiperidine oxalate, from the corresponding unsubstituted piperidine and 1-bromopentane by reflux for 12 h, m.p. 213° C.

(+−)-trans-3-(4-allyl-2-methoxyphenoxymethyl)-1-pentyl-4-phenylpiperidine oxalate, by reflux of the corresponding unsubstituted piperidine with pentyl bromide for 16 h, m.p. 116° C.

(+−)-trans-3-(3,4-methylenedioxyphenoxymethyl)-1-pentyl-4-(3-trifluoromethylphenyl)-piperidine hydrochloride from the corresponding unsubstituted piperidine by reflux for 1 h with pentylbromide. M.p. 166.6° C.

(+−)-trans-1-pentyl-3-(3-phenoxyphenoxymethyl)-4-phenylpiperidine oxalate from the corresponding unsubstituted piperidine and pentylbromide by reflux for 2 h. M.p. 77° C.

(+−)-3-(4-allyl-2-methoxyphenoxymethyl)-1-pentyl-4-(3-trifluoromethylphenyl)-piperidine oxalate, prepared from 1-bromopentane and 3-(4-allyl-2-methoxyphenoxymethyl)-4-(3-trifluoromethylphenyl)piperidine by reflux for 10 h, M.p. 130.4° C.

(+−)-3-(4-allyl-2-methoxyphenoxymethyl-1-pentyl-4-(4-trifluoromethylphenyl)-piperidine oxalate, prepared from the corresponding unsubstituted piperidine as the oxalate and pentylbromide, purified on silicagel column CH_2Cl_2/CH_3OH 9/1 as eluent. M.p. 141.2° C.

(+−)-trans-3-(4-allyl-2-methoxyphenoxymethyl)-1-butyl-4-phenylpiperidine oxalate. Preparation from 1-bromobutane and the unsubstituted piperidine by reflux for 5.5 h. M.p. 74.9° C.

(+−)-trans-3-(4-allyl-2-methoxyphenoxymethyl)-1-cyclopropylmethyl)-4-phenylpiperidine oxalate, from cyclopropylmethylbromide and unsubstituted piperidine by reflux for 2 h. M.p. 80.1° C.

(+−)-trans-3-(4-allyl-2-methoxyphenoxymethyl)-4-phenyl-1-propylpiperidine oxalate, from 1-bromopropane and unsubstituted piperidine by reflux for 6 h. M.p. 81° C.

(+−)-trans-3-(4-allyl-2-methoxyphenoxymethyl)-1-hexyl-4-phenylpipericidne oxalate, from the corresponding unsubstituted piperidine and 1-bromohexane by reflux for 144 h. M.p. 114° C.

EXAMPLE 5

(+−)-trans-4-(4-methoxyphenyl)-1-methyl-3-(3,4-methylenedioxyphenoxymethyl)-piperidine, hydrochloride

(+−)-trans-3-methoxycarbonyl-4-(4-methoxyphenyl)-1-methylpiperidine was prepared from areco-

line and 4-bromoanisole as described by Plati et. al. (J. Org. Chem. 22 (1957) 261).

9.6 g of this compound was reduced with $LiAlH_4$ (2.8 g) in dry ether (150 ml), by reflux for 6 h, giving (+−)-trans-3-hydroxymethyl-4-(4-methoxyphenyl)-1-methyl-piperidine (6.5 g) as an oil when the normal rinse-up procedure was used.

The crude product was dissolved in toluene (300 ml) triethylamine (7.7 ml) was added, and after stirring for ½ h benzenesulphonyl chloride (4.3 ml) was added, and the mixture stirred at R.T. for 5 h.

The toluene phase was washed with H_2O, dried over $MgSO_4$, filtered and evaporated to dryness resulting in 7.9 g of (+−)-trans-4-(4-methoxyphenyl)-1-methyl-3-phenylsulfonyloxymethylpiperidine as a yellow oil.

4.1 g of this oil dissolved in MIBC (200 ml) was added to a solution of sesamole (1.7 g) and NaOH (0.5 g) in MIBC (200 ml). The mixture was stirred at reflux temp. for 1.5 h. Subsequently the mixture was extracted with H_2O. The MIBC-phase was isolated and evaporated to dryness.

The resulting mass was extracted from aqueous NaOH/ether, the ether layer was isolated, dried over $MgSO_4$ and evaporated to dryness. The resulting oil was dissolved in acetone and precipitated as its hydrochloride salt by addition of excess conc. HCl-solution.

Yield 1.7 g of (+−)-trans-4-(4-methoxyphenyl)-1-methyl-3-(3,4-methylenedioxyphenoxymethyl)-piperidine, hydrochloride. M.p. 212.2° C. The identity was confirmed by the IR, NMR and MS-data.

(+−)-trans-1-methyl-3-(3,4-methylenedioxyphenoxymethyl)-4-(3-trifluoromethylphenyl)piperidine was prepared using the same reaction sequence starting from arecoline and 1-bromo-3-trifluoromethyl-benzene. M.p. 93.6° C.

EXAMPLE 6

(−)-trans-3-(2-bromo-4,5-methylenedioxyphenoxymethyl)-1-butyl-4-(4-fluorophenyl)-piperidine hydrochloride

(−)-trans-1-butyl-4-(4-fluorophenyl)-3-(3,4-methylenedioxyphenoxymethyl)-piperidine hydrochloride (1 g) was dissolved in CH_2Cl_2 (50 ml). Bromine (0.124 ml) was added dropwise at R.T. After stirring for 2 h aqueous NaOH was added, and the CH_2Cl_2 layer was isolated, dried over Na_2SO_4, filtered and evaporated to dryness. The residue was dissolved in acetone, excess conc. HCl was added, and the above mentioned bromo compound was precipitated by addition of ether. M.p. 116° C.

In exactly the same manner the following compounds were prepared from the corresponding unbrominated compounds.

(−)-trans-3-(2-bromo-4,5-methylenedioxyphenoxymethyl)-1-pentyl-4-phenylpiperidine hydrochloride, m.p. 156° C.

(−)-trans-3-(2-bromo-4,5-methylenedioxyphenoxymethyl)-4-(4-fluorophenyl)-1-pentylpiperidine hydrochloride. M.p. 105° C.

(−)-trans-3-(2-bromo-4,5-methylenedioxyphenoxymethyl)-1-(3-dimethylaminopropyl)-4-(4-fluorophenyl)-piperidine dihydrochloride. M.p. 250° C. (d).

(−)-trans-3-(2-bromo-4,5-methylenedioxyphenoxymethyl)-4-(4-fluorophenyl)-1-(2-methoxyethyl)-piperidine hydrochloride. M.p. 65° C. (hard glass).

(−)-trans-3-(2-bromo-4,5-methylenedioxyphenoxymethyl)-1-cyclopropylmethyl-4-(4-fluorophenyl)-piperidine hydrochloride. M.p. 60° C. (hard glass)

(−)-trans-3-(2-bromo-4,5-methylenedioxyphenoxymethyl)-1-(2,3-dibromopropyl)-4-(4-fluorophenyl)-piperidine hydrochloride. The crude product was purified on silicagel using CH_2Cl_2/CH_3OH 9/1 as eluent. M.p. 108° C.

(−)-trans-3-(2-bromo-4,5-methylenedioxyphenoxymethyl)-4-(4-fluorophenyl)-1-(3-thiomorpholinopropyl)piperidine dihydrochloride. The crude product was purified on silicagel using CH_2Cl_2/CH_3OH 9/1 as eluent. M.p. 241° C.

(+−)-trans-3-(2-bromo-4-(2,3-dibromopropyl)-6-methoxyphenoxymethyl)-4-phenylpiperidine hydrochloride. M.p. 98.9° C. (hard glass).

(+)-trans-3-(2-bromo-4,5-methylenedioxyphenoxymethyl)-4-(4-fluorophenyl)-1-pentylpiperidine hydrochloride. M.p. 112.3°-113.3° C.

EXAMPLE 7

(+−)-1-methyl-3-(3,4-methylenedioxyphenoxymethyl)-4-(3-trifluoromethylphenyl)-piperidine

3-methoxycarbonyl-1-methyl-4-(3-trifluoromethylphenyl)piperidine was prepared as the cis/trans mixture from arecoline and 3-bromo-trifluoromethylbenzene as described (J.Org.Chem. 22 (1957) 261). The product was purified by vacuum distillation. B.p. 90°-110° C./0.7 mmHg.

19.2 g of this compound was reduced by means of $LiAlH_4$ (4.85 g) in dry ether (325 ml) in an N_2-atmosphere by reflux for 4 h. After the normal rinse-up procedure followed by purification on a silica gel column using CH_3OH/CH_2Cl_2 (1/1) as eluent 13.2 g oil was isolated. Identified as a cis/trans mixture of 3-hydroxymethyl-1-methyl-4-(3-trifluoromethylphenyl)piperidine by means of ^1H-NMR.

The compound was dissolved in toluene (300 ml), triethylamine (13.5 ml) was added, and the mixture stirred for 1 h. Subsequently benzenesulphonyl chloride (7.5 ml) was added, and the mixture stirred at RT for 70 h. The toluene phase was extracted with H_2O; the separated aqueous layer was extracted with ether and the combined ether and toluene phases were dried with $MgSO_4$, filtered and evaporated to dryness giving 10.3 g of an oil. 5 g of the oil, which was identified as 1-methyl-3-phenylsulphonyloxymethyl-4-(3-trifluoromethyl)-piperidine by ^1H-NMR, was subsequently dissolved in MIBC (50 ml) and added to a solution of sesamol (1.9) and NaOH (0.5 g) in MIBC (150 ml). The mixture was refluxed for 2 h, stirred at RT overnight and extracted with H_2O. The MIBC-phase was evaporated to dryness, the residue was ecxtracted with NaOH/ether, the ether layer separated acetone and conc. HCl (2 ml) was added resulting in a precipitate.

This was purified on a silica gel column using $CHCl_2/CH_3OH$ 9/1 as solvent, yielding 1.1 g of (+−)-trans-1-methyl-3-(3,4-methylenedioxyphenoxymethyl)-4-(3-trifluoromethylphenyl)piperididne. M.p. 93.5° C. and 0.1 g of (+−)-cis-1-methyl-3-(3,4-methylene dioxyphenoxymethyl-4-(3-trifluoromethylphenyl)piperidine isolated as the oxalate identified by its ^1H-NMR and mass spectrum.

(+−)-3-(4-allyl-2-methoxyphenoxymethyl)-1-methyl-4-(3-trifluoromethylphenyl)piperidine oxalate was prepared from 1-methyl-3-phenylsulphonyloxymethyl-

4-(3-trifluoromethyl)piperidine and eugenol as described above by reflux for 1.5 h. M.p. 43.5° C.

EXAMPLE 8

(+−)-trans-3-(3,4-methylenedioxyphenoxymethyl)-1-pentyl-4-(4-pentyloxyphenyl)piperidine hydrochloride was prepared by refluxing 4-(4-hydroxyphenyl)-3-(3,4-methylenedioxyphenoxymethyl)piperidine hydrochloride (0.35 g) with 1-bromopentane (1.8 ml) and K_2CO_3 (1 g) in abs. ethanol (25 ml) for 2 h. The rinse-up procedure described in example 1 gave the title compound. M.p. 148.2° C.

EXAMPLE 9

(+−)-3-(4-allyl-2-methoxyphenoxymethyl)-1-methyl-4-(4-trifluoromethylphenyl)piperidine oxalate

This compound was prepared by exactly the same reaction sequence as described in example 7 using arecolin and 4-bromotrifluorobenzene as the starting materials. The intermediates were identified by means of ^{1}H-NMR and so was the identity of the product confirmed.

EXAMPLE 10

(−)-trans-4-(4-fluorophenyl)-3-(2-iodo-4,5-methylenedioxyphenoxymethyl)-1-pentylpiperidine oxalate

(−)-trans-4-(4-fluorophenyl)-3-(3,4-methylenedioxyphenoxymethyl)-1-pentylpiperidine (1.2 g) was dissolved in CH_2Cl_2 (50 ml). Silver trifluoroacetate (0.66 g) was added, followed by iodine (0.76 g) in CH_2Cl_2 added over a 10 min. period. Stirring for 24 h at R.T. The mixture was filtered, extracted with OH^-, the CH_2Cl_2-phase dried ($NaSO_4$) and subsequently evaporated to dryness. The residue was purified on silica gel and precipitated as the oxalate in acetone solution. M.p. 93.6°–94.0° C.

EXAMPLE 11

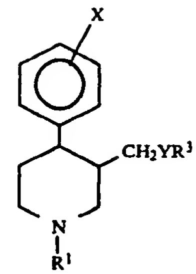
(+−)-trans-3-(4-propenyl-2-methoxyphenoxymethyl)-4-(4-fluorophenyl)-1-pentylpiperidine oxalate

3-chloromethyl-4-(4-fluorophenyl)-1-pentylpiperidine (1 g) dissolved in dry DMF was added to a solution of eugenol (0.6 g) and sodium (0.09 g) in abs. ethanol 50 ml. The mixture heated to 100° C. for 5 days. After 4 days NaH was added.

The reaction mixture was extracted with OH^-/ether, the etheral layer was dried ($MgSO_4$), evaporated to dryness and purified on a silica gel column using CH_2Cl_2/CH_3OH as eluent. Precipitated as the oxalate from acetone solution. Identified by ^{1}H and ^{13}C NMR. M.p. 128.0°–128.4° C.

We claim:

1. A method of treating anoxia, ischemia, migraine, epilepsy or head injury, which comprises the step of administering to the mammal an effective calcium-uptake-inhibitory amount of a piperidine compound selected from those having the Formula I



(I)

wherein

R^3 is 3,4-methylenedioxyphenyl, phenyl, or naphthyl, which are optionally substituted with one or more halogen, C_{1-6}-alkoxy, phenoxy, cyano, mono or poly halogenated C_{1-6}-alkyl, C_{2-6}-alkenyl, C_{1-6}-alkyl, or C_{3-5}-alkylene,

R^1 is C_{1-8}-alkyl substituted with piperidino, morpholino, thiomorpholino, dioxolanyl, or tetrahydrofuranyl, wherein the heterocyclic ring is optionally substituted with C_{1-6}-alkyl,

X is hydrogen, halogen, trifluoromethyl, hydroxy, cyano, or C_{1-8}-alkoxy,

Y is O or S;

and a pharmaceutically-acceptable acid addition salt thereof.

2. A method of claim 1 wherein the treatment is directed to the treatment of ischaemia or head injury.

3. A method of claim 1, wherein the compound is (−)-trans-1-(3-(4,4-dimethyl-1-piperidyl)-propyl)-4-(4-fluorophenyl)-3-(3,4-methylenedioxyphenoxymethyl)-piperidine or a pharmaceutically-acceptable salt thereof.

4. A method of claim 1, wherein the compound is (−)-trans-4-(4-fluorophenyl)-3-(3,4-methylenedioxyphenoxymethyl)-1-(3-(2-methyl-1-piperidyl)propyl)-piperidine or a pharmaceutically-acceptable salt thereof.

5. A method of claim 1, wherein the compound is (−)-trans-4-(4-fluorophenyl)-3-(3,4-methylenedioxyphenoxymethyl)-1-(3-thiomorpholinylpropyl)-piperidine or a pharmaceutically-acceptable salt thereof.

6. A method of claim 1, wherein the compound is (−)-trans-4-(4-fluorophenyl)-3-(3,4-methylenedioxyphenoxymethyl)-1-(3-morpholinopropyl)-piperidine or a pharmaceutically-acceptable salt thereof.

7. A method of claim 1, wherein the compound is (−)-trans-1-(1,3-dioxolyl-2-methyl)-4-(4-fluorophenyl)-3-(3,4-methylenedioxyphenoxymethyl)-piperidine or a pharmaceutically-acceptable salt thereof.

8. A method of claim 1, wherein the compound is (−)-trans-4-(4-fluorophenyl)-1-tetrahydrofurfuryl-3-(3,4-methylenedioxyphenoxymethyl)-piperidine or a pharmaceutically-acceptable salt thereof.

9. A method of claim 1, wherein the compound is (−)-trans-3-(2-bromo-4,5-methylenedioxyphenoxymethyl)-4-(4-fluorophenyl)-1-(3-thiomorpholinopropyl)-piperidine or a pharmaceutically-acceptable salt thereof.

10. A method of claim 1, wherein the compound is (−)-trans-4-(4-fluorophenyl)-3-(3,4-methylenedioxyphenoxymethyl)-1-(3-thiamorpholinylpropyl)-piperidine dihydrochloride.

* * * * *

UNITED STATES PATENT AND TRADEMARK OFFICE
CERTIFICATE OF CORRECTION

PATENT NO. : 5,208,232

DATED : May 4, 1993

INVENTOR(S) : Palle Jakobsen, Jorgen Dreger

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

Title page, item, [75]; "Dreger" should read --Drejer--.
Column 2, line 65; delete "the".
Column 3, line 38; "rate" should read -- rat --.
Column 4, line 27; "Dilution are" should read --Dilution is--.
Column 4, line 36; "significant" should read --significantly--.
Column 5, TABLE I-Continued, in the table, first column, last line, in the formula; "$-(CH_2)_3-$" should read -- $(CH_2)_3-$ --.
Column 10, line 10; "aquimolar" should read --equimolar--.
Column 10, line 12; "after few min" should read -- after a few minutes --.
Column 10, line 13; "fridge" should read --refrigerator--.
Column 12, approximately line 59; "4-phenylpiperididne" should read -- 4-phenylpiperidine --.
Column 14, approximately line 48; begin a new paragraph with "5 g".
Column 14, line 55; "ecxtracted" should read --extracted--.
Column 14, approximately line 61; "piperididne." should read -- piperidine. --.
Column 15, line 62; "injury which" should read -- injury in a mammal which --.

Signed and Sealed this

Third Day of May, 1994

Attest:

BRUCE LEHMAN

Attesting Officer *Commissioner of Patents and Trademarks*

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